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FOREWORD

THE ORIGIN AND PURPOSE OF NUTRITION REVIEWS

The science of nutrition has advanced so rapidly in recent years that professional people who need to keep abreast of current progress have experienced increasing difficulty in attempting to sift the wheat from the chaff. Clearly, there has been a very wasteful delay and no little confusion in bridging the gaps between substantial research findings and their acceptance with confidence on the part of those who deal with the public. Meanwhile, the war emergency has done much to jar the nation from its lethargy concerning the critical importance of nutrition in building and protecting human health.

A basic difficulty arises from the fact that research journals through which current findings are normally made known are so scattered and varied in nature that relatively few people have an opportunity to read and evaluate them. The factors of time, language difficulty, library facilities and limited familiarity with the criteria of good research reports tend to restrict the group that can follow the literature critically and regularly to a few who are themselves actively engaged in research.

The publication of NUTRITION REVIEWS has been undertaken, therefore, to provide an authoritative, unbiased, editorially interpreted review of the world's current research progress in the science of nutrition. The coverage of the literature will be reasonably complete and rapid, and we hope that the element of interest as well as value to the reader will not be overlooked.

The editorial staff has been carefully selected so that the publication will merit the confidence of the medical profession and other professional people who work directly with the public in the field of nutrition, including teachers, dentists, health workers, dietitians, home economists, writers and food technologists.

CHARLES GLEN KING,
Scientific Director,
The Nutrition Foundation.

FEEDING THE ARMY AND THE NAVY

It is said that our armed forces are the best fed men in the world. Data which bear witness to this fact are provided by two informative articles contributed by Colonel Paul E. Howe, Office of the Surgeon General, U. S. Army, and by Captain Ernest W. Brown (retired) of the Medical Corps, U. S. Navy (*J. Am. Med. Assn.* **120,** *93, 96 (1942)*). In addition these reports call attention directly or indirectly to some of the problems involved in feeding our soldiers and sailors.

The daily garrison ration of the Army during the period from May to October, 1941, provided each man with the following nutritional values: calories 4331, protein 131 g., fat 195 g., carbohydrate 513 g. Of the important minerals each man received 1.01 g. of calcium, 2.03 g. of phosphorus, and 25 mg. of iron. The ration provided 13,270 I.U. of vitamin A, 2.0 mg. of thiamine, 2.8 mg. of riboflavin, 29.6 mg. of nicotinic acid, and 97 mg. of ascorbic acid. Some of these values, such as those for thiamine and ascorbic acid, were corrected for moderate losses in cooking and preparation. Of course there is an element of variation and uncertainty in such losses, but they are at least receiving attention.

The data for the Navy are not so extensive. The calculated daily consumption of nutrients for each man as determined from records of the foods supplied to the personnel of the ill-fated *U. S. S. Arizona* in 1940 is as follows: calories 3089, protein 109 g., calcium 0.7 g., iron 20 mg., vitamin A 12,345 I.U., thiamine 1.8 mg., riboflavin 2.8 mg., and ascorbic acid 89 mg. No calculations were made of niacin content. The data are based on records of the food issued for a period of one year to an average of 1200 men. The calculations have been corrected on a basis of an assumed loss of 25 per cent in preparation, table waste, and spoilage, and additional corrections have been made for losses of thiamine and ascorbic acid. For both the Army and the Navy it is apparent that the nutrients meet the recommended daily allowances of the National Research Council, which emphasizes once more the truth of the opinion that the dietary requirements can be met by a well chosen diet of natural foods.

An interesting table in the report of Colonel Howe shows the relative importance of the various groups of foods and sources of the dietary essentials. Twenty-two per cent of the calories are derived from meats, fish, and poultry, 23 per cent from grain products, and 13 per cent from sugars and syrups. Forty-two per cent of the protein is provided by meats, fish, and poultry, 23 per cent by grain products, and 13 per cent by milk products. The bulk of the calcium, about 60 per cent, is derived from milk products, and surprisingly enough, the next best contribution is made by grain products, almost 12 per cent. Iron is supplied chiefly by meats, fish, poultry, grain products, and dried legumes. Vitamin A, to the extent of about 47 per cent, is supplied by the leafy and the green or yellow vegetables; butter supplies about 10 per cent, and meats, fish, and poultry about 15 per cent. Fifty-three per cent of the thiamine is derived from meats, fish, and poultry, and 15 per cent from grain products. Thirty per cent of the riboflavin is provided by the meat group, 13 per cent by fresh eggs, and 30 per cent by milk products. Sixty-five per cent of the nicotinic acid is supplied by the meat group, 10 per cent by grains, and an equal proportion by white potatoes. Ascorbic

acid is contributed to the extent of 33 per cent by the leafy green or yellow vegetables, 18 per cent by citrus fruits, another 18 per cent by white potatoes, and 10 per cent by other vegetables. Thus these surveys which are perhaps more elaborate than anything that has been done with civilian groups emphasize the well known views of nutritionists about the relative importance of different food products as sources of the various dietary essentials.

Both authors emphasize the value of adequate food and good nutrition in building and maintaining high morale of men in the service. Modern warfare exacts a heavy toll on the physical and nervous stamina of the personnel. It is good to know that the men in the service are receiving food that is nutritionally adequate according to the best available standards and it is good to know also that the medical branches of both the Army and the Navy are devoting continuous attention to nutrition, a subject which presents many difficult problems when men are required to subsist for prolonged periods of time away from their normal bases.

NIACIN CONTENT OF FOODS

All is not spinach and liver. The scientists have at last made a contribution that will arouse unstinted appreciation by the layman—a contribution to the greater enjoyment of eating chicken, hunting rabbits and munching peanuts at the ball game.

Two recent papers have greatly extended our knowledge of the niacin (nicotinic acid) content of foods. Dann and Handler (*J. Nutrition* **24,** *153 (1942)*) have analyzed numerous samples of meat, as purchased on the retail market, by their modification of the cyanogen bromide method. They found that the method gives results comparable to those obtained by the microbiological method employed by Teply, Strong, and Elvehjem, the authors of a second paper (*J. Nutrition* **23,** *417 (1942)*) which contains data for the niacin content of a great variety of important foods.

Dann and Handler found that the niacin content of the livers of beef, pork, veal and chicken was within the same range, averaging 100, 140, 123 and 152 micrograms per gram respectively. Muscle meats from the same animals and lamb contained about 60 to 70 micrograms per gram with the exception of chicken breast meat, which contained as much of the vitamin as liver, 151 micrograms per gram—welcome news for the millions who love chicken but have a different feeling about such things as spinach. Beef, lamb, and veal kidney averaged 77, 95, and 90 micrograms per gram. Rabbit tissues were high as compared to the corresponding tissues of other species. Several samples of fish were low, ranging from 9 to 35 micrograms.

In view of the fact that niacin is the most stable vitamin known, the losses reported in cooking are surprisingly large. From one-third to one-half is lost in steaming, frying, or roasting and about 60 per cent in baking. No explanation seems adequate to account for these large losses and they should be accepted with reservation until more data are available. If typical of cookery practice, losses of this magnitude will occasion great concern and a vast amount of recalculation of intake values.

It is good to see the analysis of the same cuts from several carcasses, since much information is required before an average figure can be accepted. It is noteworthy, too, that most tissues may vary as much as 100 per cent. As the authors point out, most of the data in the literature are taken from dog bioassays and are probably much too high.

In the second paper the niacin content of approximately eighty different foods is

reported, as determined by the microbiological method. Water extraction was used for all the samples except cereals, on which alkali was used to obtain an extract suitable for analysis. Fruits and vegetables as a class are poor sources of niacin, containing from 1 to 17 micrograms per g. Corn, oats, and rye range from 10 to 15 micrograms but buckwheat, barley, and wheat are considerably higher, 45 to 70 micrograms per g. As expected, most of the vitamin is present in the bran and middlings.

It is important to note that milk which is often thought of as a good specific anti-pellegra food, is actually very low in niacin, containing only 0.8 micrograms per g. Eggs are also low. Peanut butter, however, contains 186 micrograms per g. and ranks with liver as a source of niacin. These findings are of major importance in the pellagra areas especially, because they call for a new point of view in providing foodstuffs with a maximum value in terms of niacin content and economy.

SYNTHESIS OF B-VITAMINS BY INTESTINAL BACTERIA

Although the function of some of the vitamins as growth stimulants for bacteria has been recognized and, indeed, has stimulated the investigative work which led to the recognition of niacin (nicotinic acid), biotin, inositol, pantothenic acid, and other substances as dietary essentials, no extensive study has been made of the ability of these non-green, microscopic plants to synthesize the vitamins. Such information as has been available, however, indicates that this type of investigation should be productive of results of considerable practical importance to man. The synthesis of vitamins of the B-complex by yeast has been extensively studied in recent years and the results are well known. The ability of the immense bacterial population in the rumina of herbivores to synthesize thiamine, riboflavin, and pyridoxine enables sheep and cows to secure greater amounts of these factors than are contained in their feed. The early studies in this field at Pennsylvania State College, with cattle, marked an important stage in the science of livestock feeding. The intestinal bacteria can also synthesize vitamin K, which explains in part the importance of the anti-hemorrhagic vitamin for the newborn infant, whose intestinal tract is sterile.

Laboratory workers in nutrition long have been familiar with the troublesome phenomenon of refection, in which white rats are able to secure some of the B-vitamins which are withheld from their diet, by eating their feces. It is also well known that the composition of the diet has a marked effect upon the type and luxuriance of bacterial growth in the intestinal tract. Such observations have suggested that the bacterial flora of the human intestine may also be a factor to reckon with in consideration of the vitamin requirements of man. Burkholder and McVeigh (*Proc. Nat. Acad. Sci., U. S.* **28,** *285 (1942)*) at Yale University now have reported the results of what appears to be a carefully prepared program of research on the synthesis of vitamins by intestinal bacteria. They grew pure cultures of six species of common intestinal bacteria in simple media (containing inorganic salts, dextrose, asparagine, tryptophane, and cystine in distilled water) under standardized conditions and measured the amounts of biotin, riboflavin, thiamine, and nicotinic acid which they produced. The assays were made, incidentally, by microbiological methods which depend on the selection of organisms whose growth in turn is limited and quantitatively controlled by the supply of the particular vitamin under investigation.

The organisms studied were *Escherichia coli*, *Proteus vulgaris*, *Bacterium aerogenes*,

Alcaligenes fecalis, *Bacillus mesentericus*, and *Bacillus vulgatus*. For *B. mesentericus* it was found necessary to supply biotin initially and for *P. vulgaris*, nicotinic acid, because these organisms apparently are unable to synthesize these factors. The two organisms were able to synthesize appreciable quantities of the remaining vitamins that were studied, however, and the other four species of bacteria likewise produced appreciable quantities of the four vitamins when incubated at body temperature. Calculated on the basis of the amount of vitamin produced per gram of fresh cells, *E. coli*, normally a dominant organism in the human intestinal flora, produced the most riboflavin, *A. fecalis* the most thiamine, and *B. vulgatus* the most nicotinic acid. The quantities of biotin produced were small in all instances.

It was also shown that most of the vitamins were contained within the bacterial cell. Even after long continued growth only about a third of the vitamin content was leached from the bacteria into the media. Studies of the rate of vitamin production by *B. aerogenes* showed that the initial synthesis was rapid, so that not much more was produced in forty-eight hours than in fourteen and one-half hours of incubation. The failure of the synthesized vitamins to escape freely into the surrounding medium may explain the apparent inadequacy of such a source for most of the larger animals, including man.

The authors conservatively conclude that the species of bacteria studied synthesized some of the B-vitamins in greater amounts than were used in their metabolism, and that the excess accumulated in the cultures. While much more work must be done before a complete picture is obtained of the functions and practical significance of intestinal bacteria, it is evident that the vast numbers of intestinal bacteria living with us throughout life may at times play an important part in our welfare. Under certain conditions it is possible that the effects of diet in controlling the nature of our intestinal flora may assume practical importance well beyond the immediate provision of specific nutrients. Further studies of the kind reported by the Yale investigators should help elucidate some of the puzzling problems of nutrition, for example, the fact that healthy babies thrive on cow's milk, suitably modified, and have shown no signs of nicotinic acid deficiency in spite of the low content of nicotinic acid in milk, an amount considered by nutrition experts to be less than desirable. Are the intestinal bacteria responsible for this ability to get along with what seems to be a meager supply of an important dietary essential? The view that intestinal bacteria may be distinctly beneficial, contrary to the classical views of Metchnikoff, thus looms as a definite possibility.

VITAMIN D AND TOOTH DECAY

No subject in nutrition is more controversial, or more in need of clarification, than our ideas of the cause and prevention of tooth decay. The observations of McBeath and Verlin recently reported in the Journal of the American Dental Association (*J. Am. Dental Assn.* **29**, *1393 (1942)*) offer additional evidence of the effect of different forms and quantities of vitamin D on this widespread disease in which nutrition undoubtedly plays a major role. These New York investigators studied the beneficial effects of different amounts of vitamin D in the form of irradiated ergosterol (as preparations of viosterol) or of cod liver oil (as preparations of cod liver oil concentrate) on the development of dental caries in children, aged ten to twelve years, over a period of seven months. These children resided in cottages, the food materials for each kitchen

were obtained from a central storeroom, and the diet for the entire school was planned by an experienced dietitian; thus the diets were considered to be uniform and adequate. The children were divided into four groups, consisting of about 40 persons in each; there was also a control group of children who received no supplement. The supplements administered were, respectively, 400 units (U. S. P.) of vitamin D as cod liver oil concentrate, 800 units of the same, and 800 and 3200 units of vitamin D as viosterol in oil. Each of the preparations was incorporated in sweetened chocolate flavored syrup; this syrup, fortified with vitamin D, was diluted with milk, and served as chocolate flavored milk. Apparently there was no difficulty in having the children consume this beverage regularly, an item of interest because dairies selling chocolate flavored milk rarely find customers who will drink the product regularly. The vitamin D potency of the preparations was assayed both before and after mixing with the syrup, and periodic checks were made on the beverage as consumed. Several dentists cooperated in the examination of the teeth of the children both at the beginning (September, 1940) and at the end (May, 1941) of the experiment. The results were recorded in terms of the number of carious tooth surfaces, and the differences found were taken as a measure of the effect of the vitamin D supplements in the prevention of tooth decay. In all children examined there was some increase in dental caries, but there were large differences in the response of the several groups.

The children in the control group, receiving no extra vitamin D, showed on the average an increase of 4.50 carious surfaces for each child. The children receiving 400 units of vitamin D from cod liver oil showed an average increase of 2.48 carious surfaces per child; those receiving 800 units of vitamin D from cod liver oil, 1.65. The children receiving vitamin D from viosterol showed, for those receiving 800 units, an increase of 2.48 and, for those receiving 3200 units, an increase of 2.27 carious surfaces per child. The results, like many previous findings in this country and abroad, are indicative of the fact that vitamin D has a beneficial effect in the maintenance of normal tooth structure and in the prevention of the extension of dental caries, under the conditions of the experiment. Better results were obtained with 800 units of vitamin D from cod liver oil than from 400 units, but even with the larger dose there was not complete protection. Vitamin D in the form of ergosterol also afforded some protection, but the benefits resulting from 800 units were no better than those obtained with 400 units from cod liver oil. The reported effects of 3200 units from ergosterol were not as good as those obtained with 800 units of vitamin D from cod liver oil, though the differences between the results for these two groups were not statistically significant.

The observations of McBeath and Verlin not only represent a contribution to our knowledge of diet in relation to tooth protection but they also have a bearing on current views about the relative values of vitamin D from animal sources (vitamin D_3) and vitamin D from plant sources (vitamin D_2), and on the requirement for vitamin D. A consideration of the nature of the experiments of McBeath and Verlin and of the results of other investigators leads to the opinion that the present results should not be considered as an adequate basis for the claims, (1) that vitamin D_3 is markedly superior to vitamin D_2, unit for unit, for the human being or (2) that the childhood requirement for vitamin D is 800 U.S.P. units daily, unless and until these observations are corroborated and extended by investigators in other institutions. It is particularly urgent that such studies should include large numbers of children and long intervals of time. There are so many factors involved in human nutrition that the need for independent verification of most observations is essential. Especially is this

true of experiments dealing with the health of the teeth.

It is apparent from the observations of McBeath and Verlin that 800 units of D_3 is superior to 800 units of D_2, but there is evidence in the literature to the effect that differences in physiologic aspects of these two types of vitamin D are, in the human being, very small. There is also some evidence that intakes of 1500 units of vitamin D, in younger children, are not just as effective as 400 units, even though the vitamin is equally dispersed in a large volume of milk. Hence, the comparison of results with 3200 units of vitamin D_2 and those with 800 units of D_3 or D_2 may not be valid.

There are several reasons why the results of McBeath and Verlin cannot be interpreted as indicating that the requirement for growing children is 800 U.S.P. units of vitamin D daily. In the age group studied, ten to twelve years, there is theoretically the greatest growth need for calcium, and hence the vitamin D requirement at this age may be greater than it is at other ages. Better results were obtained with 800 units than with 400 units of D_2, but complete protection was not afforded with the higher intake. The development of dental caries requires time and so does the treatment, if it is to be effective. Higher dosages of vitamin D may decrease the latent period before the further development of tooth decay is arrested. The possibility remains, therefore, that with a longer period of observation the results might have been considerably different. There is also a question about the adequacy of the diet consumed by the children in the different cottages. The dietetic control was exerted from a distance, introducing the possibility that there may have been differences in cooking, food selection by the children, and the like. As Osborne and Mendel pointed out many years ago, it is necessary to take extraordinary pains to see that the only variable between groups is the one factor being studied.

With controlled diets, nutritionally excellent in all respects so far as known nutrients are concerned, except for the absence of vitamin D, Jeans and his associates at Iowa City have reported that the daily consumption of 350 units of vitamin D_3 in 750 ml. of milk, by children up to ten years of age, resulted in excellent retention of calcium and complete protection from dental caries. Differences in the amount of sunlight in different localities, the presence of variable, small amounts of fluorine in the drinking water, the amount of sugar in the diet, and many other factors no doubt are involved in the development of dental caries and hence should be controlled as far as possible in experimental studies. Small wonder that there is no general consensus of opinion as to the cause and control of tooth decay. The experiments of McBeath and Verlin, however, represent a contribution to our knowledge of the subject and their observations are a challenge to other workers in this field. There are few problems in public health that offer so much promise of value from carefully planned research as the study of dental caries.

MUSCLE DYSTROPHY AND VITAMIN E DEFICIENCY

A detailed study of the tissues of young mice born of vitamin E-deficient mothers has been made by Pappenheimer (*Am. J. Path.* **18,** *169* (*1942*)). Two hundred ninety-three newborn young, one to thirty-five days of age and from mothers maintained for several generations on a vitamin E deficient diet, were examined after careful fixation (Bouin's fluid) and staining.

Mice do not exhibit the usual signs of paralysis and muscle lesions like other experimental animals. Upon histologic ex-

amination edema of the subcutaneous and intramuscular connective tissue was the most striking observation in the mice one day old. Hyaline necrosis frequently accompanied by pyknosis and nuclear fragmentation was a common occurrence in the young mice up to about thirty-five days of age. Thereafter early calcification of the necrotic fibers and active regeneration occurred. In adult mice scattered hyaline and calcified fibers remained from the early lesions, but no progressive dystrophy of the muscles developed. No lesions of significance were found in the central nervous system. Surprisingly, in the mouse, spermatogenesis was not interfered with.

This study deserves special mention in that it adds to the mounting evidence which indicates that vitamin E is primarily involved in normal muscle metabolism. If vitamin E has any effect whatever on reproduction it is secondary. It is becoming increasingly clear that vitamin E has little if any direct effect upon the reproductive function. Clinical reports to the effect that vitamin E prevents abortion must be seriously questioned until positive experimental proof is obtained. In many cases wheat germ oil as a carrier of vitamin E was administered. It must be pointed out that wheat germ oil preparations may be extremely low in vitamin E potency and further that the wheat germ oil per se may carry dietary factors other than vitamin E which may be beneficial in certain stages of pregnancy.

Until new evidence is available the role of vitamin E in mammalian physiology must be restricted to its effect upon muscles and muscle metabolism. It no longer, in the opinion of the author, deserves the label of the antisterility vitamin.

VANADIUM, A NON-ESSENTIAL TRACE ELEMENT

Few persons who were fortunate enough to be present at the 1928 meetings of the American Society of Biological Chemists, when Professor E. B. Hart of the University of Wisconsin announced the nutritional significance of copper for the utilization of iron, will ever forget the dramatic import of his reported observations. For the first time it was evident that a vital function existed for one of the "trace elements" in nutrition, inorganic elements (other than iron and iodine) so designated because they are present in small amounts in foods and body tissues. It had been thought that the trace elements were merely adventitious components of animal tissues. Of course, it had been known for many years that copper was an essential constituent of the blue coloring matter of the blood of certain marine organisms, much as iron is an essential component of the red coloring matter of the blood of higher forms of life. Professor Hart and his colleagues showed that anemic animals restricted to milk diets would not produce hemoglobin unless the diet contained sufficient quantities of copper, or the tissues, especially the liver, of the anemic animals were relatively rich in their stores of this trace element.

Since the time of that report there have been numerous investigations of the possible functions of the different trace elements in nutrition. Experimentally zinc, manganese, fluorine, and several other elements have been shown to be of biologic importance. Vanadium is one of the elements that is not only sparsely distributed in nature, but is also rare in biological materials. Some of the lower marine forms of life however have utilized this element as an essential ingredient of their respiratory pigments. There is evidence also from *in vitro* experiments that the addition of vanadium compounds, such as sodium meta vanadate, to

suspensions of the liver of rats and guinea pigs results in an increased oxygen intake of these tissues. This fact would indicate that vanadium, a component of the respiratory pigment in molluscs, may have a function in the cellular respiration of higher forms of life. Recently Daniel and Hewston of the U. S. Department of Agriculture, and also of the Department of Biochemistry of the Johns Hopkins School of Hygiene, have made an investigation of the possible biological role of vanadium in nutrition (*Am. J. Physiol.* **136,** *772 (1942)*). An essential feature of their work has been an improvement in the method for the detection of vanadium. Earlier investigators have used electrodes which contained small amounts of vanadium; the amount of vanadium in tissues was estimated by quantitative comparison of the intensity of the vanadium lines in the spectrographs of the naked electrodes, and of electrodes containing small quantities of the inorganic part of the substance under investigation. Daniel and Hewston found that there are many other salts which tend to increase the intensity of these lines and thus give the erroneous impression that vanadium is present; hence, the results of previous investigations may be in error if the electrodes contained any trace of this element. According to their own technic, using electrodes that were proved to be free from vanadium, they found that none of the ordinary materials used for dietary experiments with animals contains vanadium, with the exception of some specimens of calcium carbonate which contained a very minute trace. Several animal tissues were examined for vanadium and these likewise showed no trace of the element by the improved technic. There is no detectable vanadium in eggs, which indicates that the chick is able to develop without the presence of this element, nor could vanadium be formed in the tissues of experimental rats or in the food ordinarily fed to these animals. No trace of the element could be detected in milk powder.

Therefore these investigators have concluded that vanadium is of no significance in the nutrition of higher animals, unless it functions in amounts of less than one to five parts per million in the ashed material of tissues, these being the limits of detection of vanadium by their method.

VITAMIN A IN LIVER

Moore and Payne of the British Medical Research Council have endeavored to furnish data relative to typical values of vitamin A for livers purchased from the butcher by the British consumer (*Biochem. J.* **36,** *34 (1942)*). Such information is of great practical importance in England at the present time, owing to decreased supplies of animal sources of vitamin A and the rationing of meats.

Two series of estimations were conducted. The first series included fresh livers obtained between March 26th and April 2nd, 1941, prior to the growth of new grass. The second assay period was chosen between September 9th and September 18th, 1941, after animals had access to fresh green pasture for the summer months.

The fresh liver fats were digested with alkali and the vitamin assays were made on the unsaponifiable fractions by means of the antimony trichloride method. Carotene did not present a problem in assaying sheep and pig livers since this precursor of vitamin A was not present in measurable amounts. Hogs and sheep have long been known to be highly efficient converters of carotenoid pigments. Selected samples of bovine livers were examined for carotene by the Zeiss photometer and corrections were made for

the potential vitamin A potency of carotene. The contribution of carotenoid pigments to the total vitamin A activity of bovine livers was extremely small.

As might be expected, the number of international units of vitamin A per gram of liver fluctuated widely. The vitamin A unitage of very young animals was low compared with that of older animals, where opportunity for storage had been greater.

Livers of cattle and pigs were usually richer in vitamin A in summer than in winter. This was not the case with sheep, since mean vitamin A values were approximately the same for both periods.

The following table summarizes the principal conclusions drawn from these studies:

Combined vitamin A and carotene values

(I. U. per g. liver)

	Winter	Summer	Mean of Summer and Winter
Sheep	450	468	459
Beef animals	89	198	144
Calves	11	66	39
Pigs	12	78	45

The distinct superiority of sheep liver over the other livers is of interest and practical value. The reason for the higher vitamin A content of sheep liver may be due to the fact that British cattle subsist on rations lower in carotene than those fed to sheep. A more efficient utilization of carotene by sheep may also be a major factor.

CARDIAC AND RENAL LESIONS AND INSUFFICIENT POTASSIUM

One of the baffling problems of medicine has been that of determining the cause or causes of cardiac failure. Earlier work of Schrader, Prickett, and Salmon and of Thomas, Mylon, and Winternitz indicated clearly that lack of dietary potassium could cause cardiac lesions. More convincing evidence has now been reported from animal studies by Follis, Orent-Keiles and McCollum (*Am. J. Path.* **18,** *29 (1942)*).

In this study 90 rats were fed a diet adequate in all known respects except for a low potassium content (0.01 per cent). Necrosis of the myocardial fibers and the renal tubular epithelium was produced. Addition of adequate potassium to the diet completely prevented the appearance of these histopathologic changes.

In the heart, microscopic inspection showed loss of striation of the individual muscle fibers by the eighth day of the low potassium diet. As early as the fifteenth day, tiny opaque grayish areas could be seen beneath the epicardium and endocardium by means of binocular lamps. There was progressive necrosis of the individual muscle fibers, nuclear atrophy and disintegration. Necrotic fibers were found also in the center of the ventricular wall but lesions were scanty in the auricular muscle. The authors report that "in some animals the process took on the appearance of a diffuse myocarditis" while other cases suggested lesions encountered in human diphtheria. By the sixth week the necrotic foci were extremely numerous, followed by connective tissue proliferation and invasion of the area by mononuclear leucocytes.

The kidneys were prominently hypertrophied. Microscopic examination likewise showed histopathologic changes about the eighth day of the experiment. The cells of the convoluted tubules underwent vacuolation, fatty degeneration and subsequent necrosis. Some tubules were greatly dilated and the lumina of some contained numerous calcified casts.

Many other organs studied showed a negative histopathology.

The mechanism by which these anatomic changes are produced is still obscure although the importance of potassium in

the normal physiology of heart and skeletal muscle is well recognized. A more complete understanding of the role of potassium in muscle metabolism might elucidate the cause of the cardiac and renal lesions produced by the low potassium diet. These results may bear an interesting relationship to the plan of restricted potassium intake now practiced in the treatment of certain forms of familial paralysis and Addison's disease.

VITAMIN CONTENT OF WHEAT

A recent study by Teply, Strong, and Elvehjem (*J. Nutrition* **24,** *167 (1942)*) fills several gaps in our knowledge of the contribution of wheat and wheat products to the dietary intake of niacin, pantothenic acid, and pyridoxine.

Four varieties of dark hard winter wheat, each grown in four different localities of Kansas and Nebraska, were analyzed. Neither varietal nor environmental differences seemed to exert a significant influence on the amount of pantothenic acid and pyridoxine present. The niacin content was apparently dependent to some extent on both the variety and the environment. However, all the above samples, and most of some 40 miscellaneous wheats, contained from 55 to 65 micrograms of niacin, 10 to 15 micrograms of pantothenic acid, and 4.0 to 5.0 micrograms of pyridoxine per g. of wheat.

Fifty samples of milled patent and clear flours indicate that the milling loss of niacin, pantothenic acid, and pyridoxine is approximately 83, 57, and 52 per cent respectively for patent flour and 64, 28, and 15 per cent respectively for the first clear flour.

Wheat germ contains only 34 micrograms per g. of nicotinic acid, 9.6 of pyridoxine, and 15 of pantothenic acid.

Thus we know that thiamine, riboflavin, and pyridoxine are concentrated in the germ portion of the wheat but niacin and pantothenic acid are not. The addition of small amounts of the germ to flour would not be an effective means of raising the concentration of the latter two vitamins in flour or bread, and it would appear that the nutritional improvement given to bread by including 5 per cent of germ cannot be attributed to the addition of these two members of the B-complex.

Niacin and pantothenic acid were determined by microbiological methods. Niacin was extracted with dilute alkali since this treatment gives results approximately 20 per cent higher than water extraction which is used in the pantothenic acid method. Further tests are in progress to determine whether this increased activity is due to a compound that is biologically active in the human body. Rat bioassays were used to determine pyridoxine.

COPPER AND COBALT IN HEMOGLOBIN PRODUCTION

While it is agreed that copper must be available before iron can be used for hemoglobin synthesis, there remains considerable confusion as to the importance of copper in practical human nutrition. Copper deficiencies have been observed in farm animals and in plants under natural conditions, but usually they are observed only in the course of rigidly controlled experiments. Probably the case for clinical deficiencies is strongest in feeding infants who are on a low-copper milk diet. The quantities of the metal needed physiologically are small and its distribution in foods is so widespread that it is difficult to imagine a natural mixed diet, calorically adequate, which would not

provide an adequate supply of the element, except perhaps in copper-deficient areas or under certain unknown conditions that might increase the requirement. Many physicians treat iron deficiency anemias (hypochromic) by prescribing iron preparations containing added copper on the basis that the copper might increase the effectiveness of iron.

Recent experiments by Robscheit-Robbins and Whipple (*J. Exp. Med.* **75,** *481 (1942)*) are of interest in this connection. Dogs that were fed a salmon bread diet were then made anemic by systematic bleeding. The animals were known not to be deficient in copper, hence the experiments were not analogous to many of the studies that have been reported, based upon copper-deficient rats. The ration provided at least 1 mg. of the element daily and the animal tissues had been shown to contain approximately normal or increased amounts. Two important demonstrations were made:

1. The addition of 5 to 15 mg. of copper daily to the salmon bread ration resulted in a moderate but irregular increase in hemoglobin production. How the increased utilization of iron was effected is not clear. Since the animals were not deficient in copper, the authors postulate that it initiated "a change in flow of the protein precursors into the hemoglobin channel—whether this change is associated with enzyme systems or other mechanisms." Larger daily additions of copper, 20 to 40 mg., frequently depressed hemoglobin manufacture.

2. When copper and iron together were used to supplement the basal ration, hemoglobin production was no greater than when iron alone was used. In these experiments, 2 to 40 mg. of copper were allowed.

These results may add weight to the concept that nothing is gained by adding copper to the diets or in the therapy of hypochromic anemia. However, some investigators will question how much can be interpreted from the failure to respond to a dietary factor known to function in minute amounts and which was already present in the experimental diet. Possibly not all patients with hypochromic anemia may be assumed to be adequately supplied with copper. The above first result is indicative of a more efficient utilization of iron when copper is supplied above levels that are adequate when there is an abundance of iron. The question deserves an exhaustive study on human subjects from many different areas, with varied dietary habits, and representing a variety of physiological and pathological states.

The second half of the study by Robscheit-Robbins and Whipple was concerned with the possible relation of cobalt to hemoglobin production. The methods used were essentially the same as in the copper experiments except that 5 to 40 mg. of cobalt were used as a daily supplement to the salmon bread. Iron was also given to some of the dogs. Cobalt not only failed to stimulate hemoglobin production, but often actually reduced the output, probably by a toxic effect. This result may seem to contradict the conclusions of many other investigators who have found that cobalt induces the formation of an excessive amount of hemoglobin and a polycythemia in experimental animals. It should be emphasized, however, that polycythemia and increased hemoglobin production are not necessarily synonymous. It is possible that the primary effect of cobalt is to stimulate more rapid production of red cells, an effect which might be difficult to detect in animals whose bone marrow had already been stimulated to increased red cell production by repeated bleedings. The fact that hemoglobin production was not favorably influenced by cobalt in these studies is not convincing evidence against a cobalt erythrocytogenic effect.

An earlier comprehensive review by

Schultze of the functions of copper and cobalt with special reference to blood formation (*Physiol. Rev.* **20,** *37 (1940)*) will interest many who are following this field of study. Almost nothing is known of the specific functions of cobalt in life processes, but the function of copper in controlling the synthesis of iron-containing enzymes as well as hemoglobin in animal tissues is very striking.

THE FOOD AND NUTRITION OF INDUSTRIAL WORKERS IN WAR TIME

The importance of the above subject and the need for competent guidance coupled with vigorous action relative to it, should be kept before laymen and scientists alike.

An interesting and authoritative "chart for action" has been prepared by the Committee on Nutrition in Industry of the National Research Council, under the chairmanship of Dr. Frank G. Boudreau who is also chairman of the Council's Food and Nutrition Board.

The report has a broader significance than the title might indicate at first thought, because the problem of providing for good nutrition in war time is basically much like the problem that we face constantly. True, there are special technological difficulties relative to foods and nutrition that are peculiar to the war emergency, but in large degree the problems that we face as we tighten our belts for the struggle are problems that we should have been giving attention to before we were in the midst of a crisis. Every reasonable protection of our physical health and mental activity is basic at all times.

The report is brief (17 pp.), factual in regard to the significance of the problem, and clearly merits the confidence and thoughtful consideration of executives as well as physicians and others who are working professionally in the field of nutrition.

The none-too-bright picture of the state of affairs as we entered the war is indicated by the following quotation:

"Of the thirty-three plants surveyed by the Committee on Nutrition in Industry during the summer of 1941, only two employed either a nutritionist or a dietitian. In one of these instances the nutritionist was attached to the staff of the medical department. She had no control over the cafeteria system. In the other, a dietitian was employed to manage the cafeteria. She was in no way connected with the medical department. The plant physician was responsible only for the purity of the foodstuffs purchased. In one plant in New England the cafeteria system, including menus, was managed by a so-called 'efficiency expert.' His qualification for the job was that he had been able to feed four thousand men in twenty minutes. He knew practically nothing about nutrition and employed no one to advise him on the subject."

The specific recommendations of the Committee are as follows:

"1. Nutritious meals of natural foods at prices the workers are accustomed to and can afford to pay should be made available in all plants engaged in production for war or defense purposes, except in small plants where the worker may obtain such meals from private sources in the free time at his disposal. Any meal served in the plant should contribute at least one-third of the daily requirements of specific nutrients recommended by the Food and Nutrition Board of the National Research Council.

2. The practice of serving food between meals to workers has given good results and is recommended. Milk, fruit and tomato juices are to be preferred as beverages, and other foods which are served should include the necessary nutrients. Thus, when bread is served it should be enriched white bread or a whole grain product.

3. Choice of foods served in the plant should be determined by a trained dietitian or nutritionist. Brief study of workers' diets will enable the dietitian to make up menus calculated to compensate for the ordinary inadequacies. The employment of a dietitian or nutritionist by the plant is recommended. In cases where this is not feasible, advice may be obtained from the state or local Committee on Nutrition.

4. Suitable educational material should be presented in connection with cafeteria service or supplementary lunches to stimulate acceptance of the meals planned or the selection of good meals when there is a choice of foods. Such material should be so planned as to lead to the development of good health habits and should avoid undue emphasis on any particular food.

5. Measures should be taken by the appropriate subdivision of government to condition nutritionally those classes of the population which are likely to become workers in war or defense industries. Such nutritional conditioning might well be carried out among organized groups such as are found in CCC camps, NYA, WPA and Defense Training Schools. The large percentage of young men found to be unfit for service in the armed forces emphasizes the need for such conditioning, for employment in war industries may be just as strenuous and in far less favorable environment than service in the armed forces. Such work, already under way in this country, should be greatly extended.

6. It is recommended that adequately controlled studies be conducted in selected war or defense industries to determine the facts concerning the influence of diet and nutrition on health, working capacity, incidence of accidents, absenteeism and the psychological state (industrial unrest).

Workers and employers who cooperate with governmental or private scientific agencies in carrying out such studies will be performing a national service. One such study is being carried out by the Los Angeles County Committee on Nutrition in Industry under the auspices of the Committee on Nutrition in Industry of the National Research Council, and others are on the way."

Copies of the report are available by writing to Dr. Frank Gunderson, Executive Secretary, Food and Nutrition Board, 2101 Constitution Avenue, Washington, D. C.

ASCORBIC ACID IN GRAPEFRUIT

Most of us wish to eat those types of fruits which possess the highest nutritive value. Plant breeders, plant physiologists, and agricultural biochemists are searching continuously for ways and means of producing foods which possess enhanced nutritional properties. Fluctuations in the ascorbic acid content of fruits and vegetables have attracted the attention of many workers and many questions have been raised as to the factors operating in the synthesis of this vitamin in plants.

Beach and Bonney tried to answer some of these questions as early as 1939. Valencia oranges varied from 36 to 63 mg. of ascorbic acid per 100 ml. of juice. These were grown in three localities. Variations within a locality were almost as large as those between localities. French and Abbott were unable to show that location in which oranges and grapefruit were grown affected the ascorbic acid content in any way. Metcalfe and associates arrived at similar conclusions regarding Texas oranges and grapefruit.

Harding and associates also called attention to seasonal changes in the ascorbic acid content of Florida oranges. They noted that oranges grown in the sun were richer in ascorbic acid than those grown in the shade. The most recent study reported by Harding and Thomas (*J. Agr. Research* **64**, *57 (1942)*) had to do with Florida grapefruit (Citrus grandis (L.) Osbeck). These studies had as their objectives the variation of ascorbic acid as affected by (1) root stocks, (2) variety, and (3) position of fruit on the tree ("outside" or exposed fruit as compared with "inside" or shaded fruit). The grapefruit used in the study were grown in a commercial grove on the Florida east coast.

Three plots of 5 trees each furnished the experimental fruits and twenty-six fruits were taken from each of the 15 trees. Thirteen fruits from each tree represented "exposed" fruit and a similar number of "shaded" fruits were picked simultaneously. Marsh grapefruit grown on rough lemon stock and on sour orange stock were com-

pared with Foster (pink) grapefruit grown on sour orange stock. Ascorbic acid was determined on the strained juice of individual grapefruit by the dye titration method of Bessey and King.

Statistical treatment of the data showed small but significant differences between "inside" and "outside" fruit, the latter being slightly higher and averaging 41.5 mg. ascorbic acid per 100 ml. of juice. The Foster variety (on sour orange root stock) gave slightly higher results than the Marsh variety, on the same root stock, an average of 42 mg. per 100 ml. as compared with 40 mg. No significant data were obtained to show differences between rough lemon and sour orange root stocks, when Marsh grapefruit sources were compared.

PYRIDOXINE AND MUSCULAR WEAKNESS

The clinical manifestations of pyridoxine deficiency in man have not been established. It is known that animals respond in different manners to inadequacies of the vitamin. Dogs, for instance, develop a hypochromic anemia while rats show impaired growth and a characteristic dermatitis. Several years ago, Spies and his associates reported that pellagrins who had been relieved of most of their complaints, by treatment with niacin, riboflavin, and thiamine, would frequently still be troubled by marked fatigue, irritability, muscular weakness, and difficulty in walking. Dramatic relief of these symptoms occasionally occurred within four hours after the intravenous administration of 50 mg. of pyridoxine hydrochloride. The suggestion that these patients also suffered from a deficiency of pyridoxine received support from observations on a separate group of pellagrins showing that they excreted less pyridoxine in urine than do normal subjects. No confirmation of these observations has been made, but they stimulated Rosenbaum, Portis, and Soskin to study the effect of pyridoxine administration to patients with marked fatigue and muscular weakness (*J. Lab. and Clin. Med.* **27**, *763 (1942)*).

Rosenbaum and his associates had their subjects perform two muscular exercise tests to the point of exhaustion under standard conditions. One of these tests required the subject, while in the supine position, to lift the extended right leg to the vertical position at the rate of twenty-four times a minute for as long as he could continue. In the second test, the patient, while sitting upright in bed, raised a ten pound weight a distance of thirteen inches at a rate of thirty times a minute. The tests were always performed twice, with a rest period of fifteen minutes, and were repeated at the same time of day. The authors make the surprising statement that no increase in muscular ability due to training was noted. During a series of control observations made on each patient, daily intravenous injections of saline were made. Changes from saline to solutions which contained 50 mg. of pyridoxine hydrochloride and back to saline again were made without the subjects' knowledge. Observations were made on twelve patients. Eight showed definite increase of muscular power following the administration of pyridoxine; of these, three were patients with hyperthyroidism, four had ulcerative colitis, and one was thought to have "so-called neurasthenia." This latter patient had been practically bed-ridden for eight years; she was sufficiently relieved of fatigue by pyridoxine so that she could be moderately active for eight hours daily. In the other four patients no improvement was noted. The diagnoses made on these latter subjects were myasthenia gravis in one, anorexia nervosa in two, and cardiospasm in one. The authors were unable to explain the

difference in response of these two groups. The eight patients who were benefited showed no evidences of deficiency disease, other than weakness, while three of the four failures manifested clinical signs of vitamin deficiencies. No evidence is presented to show that any of the subjects was actually deficient in pyridoxine. The observations certainly do not define the importance of pyridoxine for man.

RELATION OF AGE AND DIET TO PATHOLOGIC CALCIFICATION

One of the by-products of the studies on longevity initiated by McCay, Maynard, Sperling, and Osgood (*J. Nutrition* **21,** *45 (1941)*) has been the subsequent availability of these animals for study of senile changes. The data on deposition of calcium in the hearts and kidneys of rats in relation to age, source of calcium, exercise, and diet have been summarized and presented by Barnes (*Am. J. Path.* **18,** *41 (1942)*).

By grouping these experimental animals in appropriate lots and by means of stereoroentgenographs it was possible to summarize data on a large number of cases. From these studies Barnes was convinced that calcification of the heart is an increasing function of age. The most frequent site of deposition was the auricles in contrast to the ventricles and heart valves. Several important factors apparently influence the rate of calcification of the heart. Among them are exercise, form of calcium fed, and reproduction. Rats not allowed to become fat and forced to exercise showed less extensive calcification than adult rats allowed to become fat and enforced to moderate exercise. Calcium carbonate tended to cause less extensive calcification than dicalcium phosphate. Female rats subjected to the added burden of reproduction after middle life showed more extensive calcification than those reproducing earlier in life.

In the kidney the most common site of calcification was the medulla. Again a mineral supplement of dicalcium phosphate caused a calcium deposition in the kidney three times that shown by rats receiving a supplement of calcium carbonate.

ASCORBIC ACID IN TOMATOES AND CABBAGES

A recent paper by Murphy (*J. Agr. Research* **64,** *483 (1942)*) summarizes comprehensive studies conducted on the ascorbic acid content of tomatoes and cabbages during two growing seasons (1938 and 1939).

Four varieties of tomatoes were chosen for the two year study, two because they appeared to be relatively low in ascorbic acid and two because they were thought to represent varieties relatively rich in ascorbic acid. Four localities which varied in length of growing season were chosen. For this reason it was difficult to obtain comparable samples at all times. Unfortunately, as is often the case in field experiments of this type, it was impossible to assay the crops immediately after harvesting. All samples had to be shipped to the laboratories for ascorbic acid determinations.

Four varieties of cabbage were used and the ascorbic acid was assayed at bi-weekly intervals after heads had formed. The method of assay was the Musulin and King modification of the Bessey and King dye titration procedure. The author states that, for a time, samples of tomatoes and cabbages were shipped in dry ice and results were compared with unrefrigerated samples.

She reports that refrigerated tomatoes assayed somewhat higher than the unrefrigerated samples but this was attributed to stage of maturity rather than to preservation of vitamin by cooling.

With so many variables (such as variety, stage of maturity, metabolic rate, temperature, available sunshine, rainfall, soil types, inadequate sampling, enzymatic destruction of ascorbic acid during shipment, etc.) it is difficult to draw definite conclusions.

However, the author concludes, correctly, "that environmental agencies markedly influence the synthesis of vitamin C in tomatoes and cabbages, and that geographical situation is not a contributing factor except insofar as environmental conditions are consistently characteristic of that situation." Fluctuations in sunlight, rainfall and temperature undoubtedly affect ascorbic acid synthesis, causing variations which cannot be controlled experimentally, under conditions of field experimentation.

The two year study proved quite conclusively that the ascorbic acid content of tomatoes increases as the fruit matures, regardless of variety. This is not true of cabbages. In fact the ascorbic acid content of all four varieties declined as the cabbages matured and reached the marketing stage.

It would appear that varietal differences are more marked in tomatoes than in cabbages, so far as synthesis and maintenance of ascorbic acid content are concerned. The author makes a good point in stating that, for reasons just given, tomatoes should be grown that are known to synthesize relatively large amounts of vitamin C. If this is done, detrimental environmental influences should be less marked.

AVITAMINOSIS A PATHOLOGY IN DAIRY CALVES

Clinically the lack of sufficient vitamin A might well show a variety of symptoms based upon the histopathologic observations now associated with the disease. Numerous investigators of the agricultural experiment stations have contributed to this field by studies of avitaminosis A in the bovine. Constriction of the optic foramen with resulting pressure in the optic nerve has been shown to be due to lack of vitamin A in cattle. This syndrome is primarily one involving osseous tissue and it is further aggravated by an increased cerebrospinal pressure. Moore (*J. Nutrition* **17,** *443 (1939)*) has emphasized the relation of avitaminosis A in cattle to the eye symptoms, particularly nyctalopia, papilledema and permanent blindness caused by optic nerve restriction. Sutton and coworkers have observed degeneration of the germinal epithelium of the testes, absence of spermatozoa, and changes in the pituitary gland. Other workers have shown diagnostic histopathologic changes in the kidney. These reports indicate the multiplicity of the effects of a vitamin A deficiency in a species where extensive observations can be made under controlled experimental conditions.

More recently Thorp, Keener, Bechdel, and Guerrant (*Am. J. Vet. Res.* **3,** *27 (1942)*) have added further to our knowledge of this disease. These workers carefully autopsied 25 calves suffering from various degrees of avitaminosis A. In most cases enteritis was observed upon autopsy together with kidney and liver lesions. A persistent sporadic diarrhea accompanied the development of the disease and became more severe with the advance of the severity of the symptoms.

Histopathologic studies of the kidney, liver, intestines, and testes were made. Degeneration of the epithelium of the proximal convoluted tubules of the kidney was described. The degeneration was complete

in many areas and one of the peculiar responses was the proliferation of interstitial fibroblasts. The lesions of the intestine consisted of mild hyperplastic enteritis with considerable necrosis and desquamation in many cases. The mesenteric lymph glands were edematous. The liver exhibited cloudy swelling and necrosis with occasional fatty degeneration. The testes showed degeneration and necrosis of the germinal epithelium.

Since eye lesions have been prominently described in the young bovine this work would have been more complete had it included a study of the optic nerve and the eye. This phase of avitaminosis A histopathology needs further study.

The generally accepted avitaminosis A pathology is that it is primarily concerned with maintaining the functions of the epithelial cells of the body. The study herein reported as well as others indicate clearly that the anatomic relationships of vitamin A are not confined to epithelial cells alone, and that they are concerned with the metabolism of a variety of tissues of the body. Many organs and anatomical structures may be affected by vitamin A deficiency.

BIOTIN IN HUMAN NUTRITION

Biotin is one of the members of the vitamin B-complex, which in turn may be defined as the water soluble factors found in yeast. The same B-vitamins, in different proportions, are found in liver and in many other foods. Just how many factors are thus loosely grouped together is debatable; there no doubt are ten or twelve factors in all. Of these thiamine (vitamin B_1), riboflavin (vitamin G or B_2), and niacin (nicotinic acid, the factor important in the prevention of pellagra), are known to be indispensable to the human being. Among the other factors pyridoxine (vitamin B_6), pantothenic acid and biotin are known to be important for some forms of life, and presumably they are of significance to the human being. The latter inference remains to be proved in terms of controlled studies with large numbers of patients, but there is some direct evidence to support the human requirement for pyridoxine.

During 1941 a number of investigators proved the identity of (1) biotin, previously identified only as a growth stimulating factor for the yeast cell, with (2) coenzyme R, a factor involved in the growth and respiration of many strains of the legume nodule organism, Rizobium, and with (3) vitamin H, an anti-dermatitis factor for rats, chicks, and some other animals. It will be recalled also that vitamin H was at one time called the anti-egg white injury factor for rats. Brilliant investigations by several groups of workers, led by György, du Vigneaud, and R. J. Williams, have shown that the condition resulting from inclusion of large amounts of raw egg white in the diet of rats is an induced biotin deficiency due to the binding of the biotin of the diet by a protein fraction of raw egg white, thereby preventing the absorption of the vitamin from the intestinal tract. The signs produced in biotin deficient rats are severe; they are similar in some respects to the skin lesions observed in children with acrodynia, and hence there is reason for supposing that biotin is important in the nutrition of human beings.

Recently Sydenstricker, Singal, Briggs, DeVaughn, and Isbell (*J. Am. Med. Assn.* **118,** *1199* (*1942*)) have reported observations which further indicate the possible significance of biotin in human nutrition. A group of volunteers, consisting of three white men and one negro woman, consumed a diet which contained a minimal amount of biotin. This diet consisted of rice 125 g.,

white flour 80 g., farina 75 g., cane sugar 205 g., lard 32 g., washed butter 10 g., and lean beef 25 g. These foods provided 387 g. of carbohydrate, 21 g. of protein, and 32 g. of fat with a caloric value of 1960 calories. The diet also included 200 g. of dehydrated egg white. This item furnished an additional 928 calories from the 160 g. of protein and 32 g. of fat which it contained, thus giving a total value of 2888 calories daily for each person. The egg white was administered in solution in divided doses at each meal. It was calculated that the egg white provided 10 mg. of riboflavin in each 100 g. The following vitamin supplements were administered: thiamine hydrochloride 6 mg., riboflavin 9 mg., nicotinic acid 75 mg., pyridoxine 5 mg., and calcium pantothenate 5 mg. There was also given 75 mg. of ascorbic acid, 5000 units of vitamin A, 1 g. of ferrous sulfate, and 1 g. of calcium lactate. Thus the diets were complete in known nutritional factors, save for biotin and possibly such factors as inositol and p-aminobenzoic acid.

All these subjects were in good health at the beginning, but after three or four weeks' feeding on this controlled diet all four persons developed a fine scaly dermatitis, which later disappeared spontaneously. In the seventh week one patient developed maculosquamous dermatitis of the hands, arms, and legs. At this time also all the patients developed a peculiar grayish pallor of the skin. This was interpreted by the investigators as evidence of a peripheral vasoconstriction. The three men developed atrophy of the lingual papillae of the tongue but the negro patient showed no tongue changes until the fourteenth week of the experiment. None of the characteristic tongue lesions observed in riboflavin or nicotinic acid deficiencies was observed in these patients. The nervous symptoms observed after the fifth week of the experiment were strikingly similar to those reported by induced thiamine deficiency in man. There was mild depression followed by extreme lassitude, sleeplessness, and other symptoms. There was loss of appetite, especially during the last three weeks of the experiment. Electrocardiographic changes also were similar to those which have been observed in thiamine deficiencies. Despite the administration of iron the examination of the blood showed a deficiency in hemoglobin content, and in the number and size of red blood cells. Determination of the biotin excreted in the urine showed, as might be expected, a marked decrease; at the end of seven and eight weeks the patients excreted 3.5 to 7.3 micrograms of biotin in twenty-four hours as compared with an excretion of 29 to 62 micrograms in persons on an ordinary diet.

Treatment with a biotin concentrate in dosages varying from 75 to 300 micrograms brought about prompt relief. The minimum amount that seemed to be desirable for dosage purposes was 150 micrograms daily. After three to five days the depression, muscle pain, precordial distress, and loss of appetite had been abolished. The ashy pallor disappeared in four days. The authors believe it is significant that the signs and symptoms which developed were very similar to those seen in some cases of spontaneous avitaminoses. While these observations need confirmation and further elaboration, there seems to be little doubt that biotin is of importance in the nutrition of the human being. But it is also apparent that an adequate diet which provides ample amounts of the better known members of the vitamin B-complex—thiamine, riboflavin, and nicotinic acid will probably contain sufficient biotin, assuming that the supply is not reduced by egg white. Further investigations no doubt will make clear the nutritional and possible clinical significance of this interesting member of the water soluble B-vitamins.

MILK SOLIDS AND BREAD ENRICHMENT

Some practical experiments have been reported by Mitchell, Hamilton, and Shields (*Bakers' Weekly* **114,** *27 (1942)*) concerning the nutritive value of various breads. The value of adding 6 per cent milk solids to the bread was the special object of the experiments. The growth rate of rats on the various bread diets was chosen as the principal criterion of the better bread. The results may be summarized as follows:

(1) 6 per cent milk solids added to white bread or enriched bread proved superior to an enriched white bread. (2) 6 per cent milk solids added to enriched white bread proved superior to adding calcium and riboflavin. This bread proved equal to whole wheat bread. (3) 6 per cent milk solids added to whole wheat bread proved definitely superior to whole wheat bread itself. (4) The "better bread" as judged by growth criteria, was also the bread of choice when the rats were allowed unrestricted access to the breads.

Chemical analyses of the rats warrant, in the opinion of the authors, the following conclusions:

(a) "The presence of milk solids in the bread formula, or of added calcium salts, brought about a more complete calcification of the bones."

(b) "Milk solids in bread, as compared to enriched bread, induced a greater store of riboflavin in the body. Whole wheat bread behaved similarly."

(c) "Milk solids, although contributing very little niacin (nicotinic acid) to a bread formula, seemed to improve the retention within the animal body of niacin added as such to the bread."

(d) "The thiamine content of rats raised on unenriched milk solids bread was distinctly less than that of rats raised either on whole wheat or enriched bread."

This work does not purport to confirm or deny the validity of the enrichment policy, in fact the authors state that the enrichment of bread with thiamine, niacin and iron has a purpose quite distinct from the incorporation of milk solids and cannot substitute for it. Their work clearly demonstrates however, the distinct nutritive value achieved by including 6 per cent milk solids in the formula of either white or whole wheat bread. The best breads contain both the enriching elements and milk solids.

VITAMIN A THERAPY OF EXPERIMENTAL HYPERTENSION

Hypertension of a persistent nature can be produced experimentally by occlusion of both renal arteries, or by occlusion of one renal artery and excision of the other kidney. Such a procedure is generally referred to as the "Goldblatt technique" after Dr. Harry Goldblatt who designed an adjustable silver clamp and perfected the procedure of applying it to the renal arteries with resultant hypertension. Dogs rendered hypertensive by this method have served for many important studies on experimental hypertension. But it should be emphasized that there is not yet general agreement as to whether this type of experimental hypertension is comparable to essential hypertension in man. There is considerable evidence that the latter differs from hypertension associated with organic renal lesions or mechanical obstruction to flow in the main renal arteries, and this point should be kept in mind especially in evaluating reports of therapy of hypertension.

Using the Goldblatt technique, Wakerlin, Moss, and Smith (*Science* **96,** *161 (1942)*) rendered five dogs hypertensive, and after a five to eight month period of stabilization, treated three of them with daily oral doses

of vitamin A. Each received 200,000 I.U. of vitamin A daily in sesame oil for the first three months and then 400,000 I.U. daily for a second three month period. The remaining two dogs served as controls and received equivalent amounts of plain sesame oil by mouth.

Striking reductions in blood pressure were reported for each of the three dogs receiving vitamin A. No toxic effects from the vitamin A therapy were noted. The authors point out that this does not rule out the possibility of their eventual appearance. The two dosages used were, according to the authors, less than one-twentieth and one-tenth of the amounts reported toxic for rats by some workers and less than one one-hundredth and one-fiftieth of the toxic levels reported by others.

The two control dogs showed no significant changes in their hypertension and the authors state they have never seen spontaneous blood pressure decrease, similar to the changes observed in the vitamin A treated dogs, "in 75 renal hypertensive dogs during the past three years."

Wakerlin and his associates point out that none of their dogs has shown any evidences of vitamin A deficiency. It seems quite possible that the observed effect of vitamin A upon experimental renal hypertension may prove to be a pharmacologic one and may be shown to an even greater degree by substances having little or no vitamin action. The discovery of a pharmacologic action for vitamin A would not be without precedent in the vitamin field. Nicotinic acid has a histamine-like action upon the small blood vessels, not related apparently to its function as a component of coenzymes I and II. The strong reducing activity of ascorbic acid may account for its beneficial effect in the prevention and treatment of arsphenamine poisoning. Similarly the beneficial effects described for pyridoxine in the treatment of certain neuromuscular disorders are best explained by ascribing a pharmacologic action to the vitamin in these conditions.

B-VITAMINS AND GASTROINTESTINAL MOTILITY

That deficiency of certain of the B-vitamins leads to abnormalities of gastrointestinal secretion, absorption, and motility is well known. Diarrhea was early recognized as one of the cardinal manifestations of pellagra and recent roentgenological studies have revealed that multiple deficiencies of the vitamin B-complex in man are accompanied by distinct changes in motility and tonicity of the gastrointestinal tract. Vitamin deficiency states in animals have revealed similar changes but information concerning which of the B-factors might be chiefly responsible for the altered physiology is far from complete. Martin, Thompson, and Carvajal-Forero have studied just this problem (*Am. J. Digest. Dis.* **9**, *268* (*1942*)). They placed young dogs on a highly purified synthetic diet which consisted of vitamin-free casein, sucrose, butterfat, U.S.P. salt mixture, and cod liver oil. The following eight crystalline vitamins of the B-complex were used in various combinations to supplement the basal ration: thiamine, riboflavin, pyridoxine, choline, niacin (nicotinic acid), calcium pantothenate, inositol, and para aminobenzoic acid. Biotin was not used. Gastrointestinal motility was studied fluoroscopically after barium sulfate was introduced into the stomach. Observations were made at weekly intervals on each animal two or more months after the dietary regimens had been started. Only six of the many possible vitamin supplement combinations were tried, but certain conclusions seemed evident:

1. Animals fed the basal ration plus all

eight of the crystalline B-vitamins continued to have normal gastrointestinal motility patterns.

2. When all of the vitamin B factors were omitted, or when thiamine and riboflavin alone were allowed, definite changes occurred: hypermotility of the small intestine, segmentation and hypomotility of the colon, and diminution in the contents of the intestinal tract in a manner which suggested a disturbance of the normal secretory mechanism.
3. Animals given all factors except pantothenic acid showed a syndrome characterized by increased gastric emptying time with pylorospasm, marked segmentation of both the small and large intestines, hypertonicity with hypomotility, alternation of ribbon-like segments with dilated loops, frequent formation of gas, presence of fluid levels.
4. It is possible that inositol, choline and pyridoxine may also function in the maintenance of normal gastrointestinal function.

The authors stress the fact that the omission of either pantothenic acid or inositol brought about similar changes in the gastrointestinal motility pattern. However it is difficult to evaluate the role played by inositol since all of the work on this factor was complicated by the simultaneous lack of other vitamins. The literature is replete with evidence of the dangers involved in drawing such conclusions from studies of multiple deficiencies. Thus any decision as to the function of inositol in gastrointestinal physiology or elsewhere should await the production of a simple deficiency of inositol. It has not yet been shown whether or not this factor is essential in the nutrition of the dog.

It is surprising that thiamine and niacin were not observed to alter intestinal function, since both clinical and experimental observations with deficiencies of these two vitamins have indicated such a relationship. However, as the authors point out, they did not produce either a pure thiamine or niacin deficiency; hence they reserve judgment as to the function of these two substances in maintaining normal physiology of the intestinal tract. Extension and confirmation of these studies should be made so that the results can be more definitely accepted, including consideration of their usefulness in the management of deficiency diseases in man.

VITAMIN K AND ABORTION

It is now well established that the blood of infants at birth usually contains less than the normal amount of prothrombin, and that the deficiency becomes accentuated during the neonatal period. When the prothrombin values fall low enough, hemorrhagic disease of the new-born results. That this lowered prothrombin is related to a lack of vitamin K is evident since the administration of vitamin K is followed by a prompt return of the prothrombin level to normal. While they were unsuccessfully attempting to produce hemorrhagic disease of the newborn in experimental animals, Moore, Bittinger, Miller, and Hellman (*Am. Jour. Obst. and Gynec.* **43,** *1007 (1942)*) noted that rabbits fed a diet deficient in vitamin K invariably aborted during the first or second trimesters of pregnancy. Their animals were fed diets made up of dried egg white or acetone extracted casein, wheat starch, cottonseed oil, salts (McCollum 165), acetone extracted yeast, agar, cod liver oil, germinated wheat oil as a source of Vitamin E, ascorbic acid, and acetone extracted alfalfa powder. Control animals were fed the same ration except that the alfalfa was not extracted with acetone. All

the rabbits had carried a normal pregnancy to term before the experiment began. Forty days after the special diets had been started, the animals were mated. Controls had normal pregnancies but all of the other rabbits developed vaginal bleeding and aborted on the eighth to fourteenth days following mating. After several weeks, pregnancy was again initiated, but with the same results. Several animals died from hemorrhage; others were sacrificed for study. Two rabbits were continued on the deficient ration but with 1 mg. of 2-methyl-1,4-naphthoquinone added every other day. They were again mated after three weeks and normal pregnancies resulted. Microscopic examination of the placenta from animals that had aborted showed the presence of recent and old hemorrhage in the decidual plate, a change which is histologically identical with that seen in retroplacental hemorrhage associated with human abortion. It is of interest that the experimental animals developed no other hemorrhagic manifestations. The conclusion that the abortions observed resulted because of hypoprothrombinemia secondary to vitamin K deficiency seems justifiable. No instances of retroplacental hemorrhage in women have yet been related to hypoprothrombinemia, and in the human there may be no causal relationship. But the work of Moore and his associates will certainly prompt a study of that possibility.

THE HUMAN THIAMINE REQUIREMENT

The term "human requirement" is not easy to define, but there is increasing agreement that it should be based upon reasonably generous provision for good health rather than upon a bare allowance to protect from obvious and specific illness.

Williams, Mason, Smith, and Wilder (*Arch. Int. Med.* **69,** *721* (*1942*)) induced thiamine deficiency with diets that provided 0.45 mg. of the vitamin daily. Elsom, Reinhold, Nicholson, and Chornock (*Am. J. Med. Sc.* **203,** *569* (*1942*)) noted that three subjects with daily thiamine intakes of 0.38, 0.50, and 0.52 mg. respectively, developed early symptoms of thiamine depletion, while two other individuals remained symptom-free with 0.61 and 0.646 mg. allowances. Melnick (*J. Nutrition* **24,** *139* (*1942*)) found that women taking 0.7 mg. and men taking 1.0 mg. of the vitamin showed no evidences of depletion. The minimal requirement for thiamine, therefore, would seem to be between 0.52 and 0.7 mg. daily for women. Slightly greater needs are implied for men.

Before describing the experiments of Williams and of Melnick *et al.* which have sharpened our knowledge of human thiamine requirements it should be stated that the requirement is greatly affected by carbohydrate intake. This is coupled with the fact that thiamine functions as a component of an enzyme, cocarboxylase, which is concerned with carbohydrate metabolism. The earlier tendency to relate thiamine requirement to body weight is probably not valid except insofar as body weight is an indication of caloric need or intake.

Studies of urinary excretion have made possible more exact definition of thiamine needs. Melnick, for instance, noted that normal subjects subsisting on a daily intake of 1 mg. of thiamine respond promptly to additions of thiamine by excreting larger amounts. Deficient subjects do not. The 1 mg. allowance, therefore, is probably sufficient to saturate subjects to such an extent that there is no need for them to conserve added amounts. Furthermore, normal subjects show a diurnal variation in thiamine excretion, with the greatest output after meals. Deficient subjects were observed to retain the dietary thiamine to such an extent that diurnal variations do

not occur. With an oral clearance or tolerance test, using a 5 mg. dose, Melnick found that deficient subjects, after having been saturated with thiamine, excrete six times more of the test dose than they had eliminated when depleted. On the other hand, when normal subjects, fed a constant diet supplying 1.07 mg. of thiamine per day, were saturated by receiving 10 mg. of additional vitamin daily for 3 to 6 weeks, their response to the test dose was no greater than it had been before the saturation period. The dietary allowance of 1.07 mg. was therefore considered to be adequate. Lastly, Melnick studied the response to oral test doses of two groups of normal subjects: (1) males receiving approximately 3000 calories and 1.0 mg. of thiamine, and (2) females receiving approximately 2000 calories and 0.7 mg. of thiamine. On these diets the males excreted an average of 0.20 mg. and the females an average of 0.09 mg. of thiamine per day. The latter figure is moderately low and suggested that the intake of 0.7 mg. was close to the minimal point. The excretion following an oral test dose was satisfactory in both groups, however, indicating that tissue saturation with the vitamin had been established. From these results, Melnick concluded that the minimal requirement of thiamine is approximately 0.35 mg. per 1000 calories. However, in order to allow a factor of safety, he suggested that this figure be increased by 50 per cent to 0.50 mg. for each 1000 calories of the diet.

In a similar investigation, Williams and his associates studied six subjects, three of whom had been maintained for one hundred sixty-nine days on a standard diet which contained less than 0.45 mg. of thiamine in the daily allowance, and three who in addition to the standard diet had received a supplement of 7.5 mg. daily for thirty-seven days. The first group was relatively depleted and the second was initially near saturation. All six subjects were then maintained on identical thiamine intakes which initially provided 0.4 mg. of the vitamin but which were increased slowly by increments of 0.2 mg. at a time. The urinary excretion of both groups soon became identical, and the first significant increase in excretion occurred when the intake was raised from 0.4 to 0.5 mg. per 1000 calories of food. The excretion studies, therefore, indicated that 0.4 mg. of thiamine per 1000 calories was the "minimal" requirement for these subjects, but all symptoms of thiamine depletion did not disappear until 0.5 to 0.6 mg. were given for each 1000 calories. No beneficial effects were noted from giving amounts of thiamine greater than 1.0 mg. for every 1000 calories of the diet.

Results from both studies suggest that: (1) the minimum daily requirement of man for thiamine is approximately 0.5 mg. per 1000 calories, and (2) the optimal requirement is probably between 0.5 and 1.0 mg. per 1000 calories. Urinary excretion studies are not infallible but the above estimate would seem to be close approximations of the truth at least. It would be highly desirable to also have knowledge of tissue concentrations of thiamine, but the practical difficulties in the way of obtaining these are obvious though not insurmountable.

VITAMIN DEFICIENCY AND WERNICKE'S SYNDROME

In 1881 Wernicke described a clinical syndrome characterized by clouding of consciousness, varying ophthalmoplegias, and ataxia. The pathology in this disease is largely confined to the gray matter of the brain surrounding the ventricles. It is characterized by small foci of degeneration, deformities of the blood vessels, and frequently by small hemorrhages into the substance of the brain. Most cases reported

have occurred in inebriates, and alcoholism gradually came to be accepted as the cause, in spite of the fact that many instances of the disease which occurred without any relation to alcoholism have been reported in the literature.

The demonstration by Alexander (*Tr. Am. Neurol. A.* **64,** *135* (*1938*)) that the pathology of Wernicke's syndrome in man is the same as that of a syndrome which developed in their thiamine deficient pigeons has stimulated a number of workers to investigate this syndrome from the standpoint of a possible nutritional causative agent, other than alcohol.

From their study of 34 clinical cases, Bueding, Stein and Jolliffe (*Arch. Neurol. & Psychiat.* **47,** *215* (*1942*)) have come to the conclusion that the syndrome as described by Wernicke represents a combination of nutritional deficiencies. Pellagra, encephalopathy induced by nicotinic acid deficiency, riboflavin deficiency, and scurvy often superimpose themselves and complicate the syndrome. Each one of these conditions requires specific therapy. The paralysis of the external ocular muscles responds to treatment with thiamine but not to nicotinic acid, riboflavin, or pyridoxine. It is invariably preceded or accompanied by acute peripheral symmetrical polyneuropathy, a condition practically always associated with thiamine deficiency.

Thiamine pyrophosphate is essential in the cellular enzyme system for the metabolism of pyruvic acid. In acute thiamine deficiency in man the fasting pyruvic acid content of the blood tends to be higher than normal. This tendency toward an abnormally high content of pyruvic acid in the blood can be demonstrated more clearly following the ingestion of a standard amount of glucose.

Wortis *et al.* obtained pyruvate curves following the ingestion of glucose on 27 normal subjects and 7 patients with Wernicke's syndrome. Fasting blood pyruvate levels were obtained in 4 additional patients. The fasting blood level of pyruvate was elevated in all patients with the syndrome. In the 7 patients that were subjected to the additional stress of metabolizing ingested glucose, the maximum rise in blood pyruvate was not only greater than in normal subjects, but the elevation above the fasting level was maintained for at least four to five hours; normally the fasting level is reached within three hours. After therapy with thiamine, the fasting level of blood pyruvic acid rapidly returned to normal, but the pyruvic acid curve following ingestion of glucose returned to normal only after prolonged treatment.

A logical conclusion from these studies is that Wernicke's syndrome is characteristically associated with a disturbance in pyruvic acid metabolism and with thiamine deficiency. Thiamine therapy was found to cure the ocular palsies and often improved the mental status. However, the complete syndrome as described by Wernicke is frequently associated with a lack of one or more additional nutritive essentials. Wortis and his associates therefore advocate, in the treatment of this condition, "a high calorie, vitamin-rich diet, with other vitamin concentrates in addition to thiamine." They state that, in the absence of complications sufficient in themselves to cause death, they have never had a fatality where this treatment was employed.

THE ADEQUACY OF PURIFIED DIETS

Maintenance of the normal life span, satisfactory growth rate, maximum size and strength, normal behavior and resistance to disease, and the ability to reproduce and to rear successive generations are the criteria by which the adequacy of a diet for any

particular animal must be judged. Many investigators have reported purified diets that have satisfied one or more of these criteria for their experimental animals. Few, if any, have been successful in compounding purified diets that meet *all* of the criteria for adequacy. The deficiency in the best purified diets is commonly most obvious in their failure to assure normal reproduction and lactation and to maintain successive generations of the experimental animals in optimal health.

Rogers, McElroy, Cowgill (*Science* **95**, *203* (*1942*)) report on the successful rearing of a second generation of mice on a purified diet. Their basal ration consisted of casein, Cerulose, Crisco, Osborne and Mendel salt mixture with added zinc carbonate, agar, wheat germ oil and 3 per cent rice polish filtrate factor II. This basal mixture was supplemented with cod liver oil concentrate, thiamine, riboflavin, pyridoxine, nicotinic acid, calcium pantothenate, choline, para-amino benzoic acid and inositol.

Of the 5 males and 9 females placed on the diet at weaning all but 2 females were alive and well one hundred and eighty-four days after being placed on the purified diet. Three of these females were mated with a sibling male. One had 3 litters with 10 live and 4 dead young, but did not lactate until the third litter was born on the one hundred and fifty-seventh day of the experiment. She raised to weaning 3 of the 4 young in this litter.

The other two females had litters totaling 10 live and 1 dead young on the fifty-fifth day. Both females lactated and 8 of the young were raised to weaning and placed on the experimental diet. All of the 4 young females included in this group of 8 mice were mated with 2 male siblings. Ten of the 16 offspring were raised to weaning and were in good condition at forty-one days of age.

In view of the known difficulty in raising mice on purified rations, the work of Rogers and associates is noteworthy. However it seems rather obvious that their successes were accompanied by quite a few instances of failure in reproduction and lactation, even though the ration contains 3 per cent of crude material, the rice bran filtrate besides the natural fats. Such studies emphasize the difference in the nutritional requirements of closely related species, since rations containing no vitamin supplements other than crystalline materials have been shown to produce reasonably good, though perhaps not optimum, reproduction and lactation in the rat. The authors state that attempts to duplicate their results with the same diet on another strain of mice have been unsuccessful to date. Thus the probability of a difference in nutritional requirements among strains of the same species is shown.

CONVULSIVE (EPILEPTOID) SEIZURES OF NUTRITIONAL ORIGIN IN RATS

Many research workers have observed epileptoid seizures in rats subjected to severe vitamin B_1 deficiency, but little progress has been made in correlating epileptiform seizures in man with specific nutritional deficiencies. Since nutrition plays a role of recognized importance in clinical practice, however, each new lead supplied by well controlled animal experimentation provides a basis for a new approach to the problem in clinical investigations. Lepkovsky, Krause and Dimick (*Science* **95**, *331* (*1942*)) have observed a fairly high incidence of convulsive seizures among rats six to eight months of age when subjected to pyridoxine (vitamin B_6) deficiency. The English in-

vestigators, Chick, Sadr and Worden (*Biochem. J.* **34,** *594 (1940)*) had previously observed similar seizures in pyridoxine deficient rats.

Following the initial report of Chick *et al.*, clinical trials of pyridoxine in the treatment of human epilepsy were instituted. These trials are being continued in several clinics in this country and it is perhaps too early to arrive at any definite conclusions concerning the efficacy of the vitamin in this condition. However it is safe to say that the work to date does not hold much promise for this method of treatment.

Patton (*J. Comp. Psych.* **31,** *215 (1941)*) and King, Karn and Patton (*Science* **94,** *186 (1941)*) observed epileptoid seizures in rats under a variety of controlled experimental conditions. Their studies showed that exposure to noise could serve as a mechanism of inducing the onset of convulsions under relatively mild conditions of deficiency and over a wide age span. The nutritional state of the animals played a dominant role in their susceptibility. Vitamin B_1 deficiency, vitamin B-complex deficiency and simple inanition were predisposing factors. It is evident from their work that too great emphasis should not be placed upon the specific role of a single nutrient in sensitizing the animals to convulsive seizures.

THE NUTRITIVE EFFICIENCY OF ALFALFA VS. GRASS

Cravens, Holmes, Halpin, and Elvehjem (*Poultry Sci.* **21,** *301 (1942)*) completed three experiments where grain and grain millfeeds were fed to laying hens for the purpose of determining the supplementary value of alfalfa leaf meal, or dehydrated cereal grass upon egg production and reproduction. In all cases White Leghorn pullets were used to test the effect of these supplements upon egg production in direct comparison to the performance of pullets fed a laying ration composed largely of grain and grain by-products. Eggs from these birds were incubated throughout the year at bi-weekly intervals. The records of egg production, per cent hatch, and embryonic failures were kept.

The results indicated that rations composed largely of grains and grain products, minerals, and fish oils were deficient in some factor or factors which were supplied by alfalfa leaf meal but to a lesser extent by dried cereal grass. Alfalfa leaf meal carried some dietary factors in addition to riboflavin which is essential for embryonic development. Neither alfalfa leaf meal nor dried cereal grass caused any marked increase in egg production. A seasonal decline in hatchability occurred during the fall and winter months. Two per cent of alfalfa leaf meal in the ration prevented this slump while cereal grass was much less effective.

These experiments are interesting in the face of a growing belief among laymen and others that any green material will correct any diet. Witness the large consumption of lettuce and "greens" for example, and the development of dehydration of young grasses on a commercial basis for dietary purposes.

There is no doubt that young grass is high in nutritive quality but young grass may be deficient in certain factors necessary for the correction of a given diet. Green foods are especially rich in carotene, riboflavin and vitamin K. Other factors are no doubt present in variable quantities also. But just as in these experiments, alfalfa leaves may supplement a given diet more effectively than dehydrated young grass. The place of the latter in the human diet still remains to be determined by careful experimentation.

VITAMIN A IN TUBERCULOSIS

A group of investigators in Rochester, New York, Breese, Watkins, and McCoord (*J. Am. Med. Assn.* **119,** *3 (1942)*) have studied the absorption of vitamin A in persons with tuberculosis. They tested 29 patients exhibiting variable degrees of intestinal symptoms associated with severe pulmonary tuberculosis and found that the absorption of vitamin A was markedly below normal. The greater the degree of weight loss and the more severe the intestinal symptoms the poorer was the ability of these patients to absorb vitamin A.

The technic of performing these tests was to give the patient a known amount of vitamin A in the form of a concentrated fish liver oil. A convenient dosage is 7000 U.S.P. units of vitamin A for each kilogram of body weight. Samples of the blood were taken before the oil was given and at intervals of four, eight, and twenty-four hours after the ingestion of the oil. These specimens then were analyzed chemically for their content of vitamin A. The increase in concentration of vitamin A in the blood was taken as a measure of absorption. Tests performed on 25 presumably healthy adults gave a normal curve for comparison. The maximum rise of vitamin A in the blood, in terms of Evelyn Photoelectric Units, averaged 354; the average rise for the 29 patients with tuberculosis was 160. Thirteen of these patients had moderate to severe intestinal symptoms and the average value for them was 127; 16 patients had mild intestinal symptoms and the average rise in their blood level of vitamin A was 243 units. The differences were shown to be statistically significant.

The explanation of the poorer absorption of vitamin A in severely sick tuberculous patients is not clear. The Rochester investigators observed in the intestines of their patients whom they were able to examine after death no gross or microscopic lesions which were of such a nature as to lead one to expect interference with the absorption of fat or fat soluble vitamins.

It long has been recognized that patients with tuberculosis require an excellent diet. Experimentally it has been shown that the vitamin C content of the blood is low in such patients unless large amounts of vitamin C are administered. The present observations afford some experimental basis for the clinical teaching that the vitamin A content of the diet as well should be above the average requirement for healthy persons.

AVIAN AND HUMAN THIAMINE DEFICIENCY

Thiamine deficiency in humans is an unsatisfactory clinical entity. The various forms encountered, the inconstancy of certain clinical signs, and in many cases of polyneuropathy the seemingly poor results obtained by thiamine therapy are confusing to the physician. A careful study of thiamine deficiency in birds shows that many of these variations can be accounted for on the basis of the rate of production of the deficiency and the extent to which slowly reversed pathological changes have taken place.

In previous studies (*J. Exp. Med.* **71,** *683 (1940); J. Nutrition* **22,** *77 (1941)*) the outward manifestations of thiamine deficiency in pigeons were found to vary with the speed of onset of the deficiency. Similar variations were found in the extent of degeneration of nerve fibers in both the peripheral and central nervous system. Acutely deficient birds generally showed a few degenerating fibers on post mortem examinations but these were sometimes absent even in very acutely deficient pigeons. When the ration was only partially deficient in thi-

amine, permitting a more chronic onset of the deficiency disease, the development of symptoms was invariably accompanied by degeneration of the peripheral nerves, first of the large nerve fibers and later of the medium-sized fibers, the small fibers usually remaining intact. Well defined and localized degeneration was also present in the brain and spinal cord.

When sufficient thiamine was added to the diet, with or without other members of the B-complex, the peripheral nerve fibers tended to regenerate and normal clinical behavior was restored to the degree that regeneration occurred.

In recent papers Swank and Prados (*Arch. Neurol. Psychiat.* **47,** *97 (1942)*); Prados and Swank (*Ibid.* **47,** *626 (1942)*) the following observations were made: "(1) the first neuronal histologic change in thiamine deficient pigeons is degeneration of the distal part of the axon, and changes in myelin are secondary to this; (2) degeneration proceeds centralward and is accompanied by slight shrinkage or sclerosis of the cell body; (3) the large fibers degenerate first and the medium later, the small fibers usually remaining intact, and (4) opisthotonos (the characteristic manifestation of acute thiamine deficiency in pigeons) may not be attended by any definite neurologic lesions." The finding, in moderately acute deficiency, of degeneration in the sensorial epithelium of the labyrinth and in the central endings of the vestibular nerve fibers led the authors to conclude that opisthotonos is due to a selective release of the central vestibular centers from labyrinthine control. In chronically deficient pigeons without opisthotonos all central and peripheral terminations of the vestibular nerves are moderately degenerated; no preponderant site of degeneration is present. The number and size of the hemorrhages found in the brains of deficient pigeons were found to vary with the degree of acuteness of the onset of the deficiency and such hemorrhages were invariably preceded or accompanied by degenerative changes in neighboring neurons. It is probable that the hemorrhages are secondary to local changes in the surrounding brain tissue resulting in dilatation and abnormal permeability of the small vessels.

On the basis of curative experiments, neurons affected histologically by thiamine lack are divided into those which return to normal when thiamine is given and those which continue to degenerate. Fibers which have fragmented probably continue to degenerate.

Thiamine deficiency in man may manifest itself in a variety of ways, e.g., anorexia and neurasthenic symptoms, multiple neuropathy, central neuropathy (Wernicke's syndrome), and cardiovascular dysfunctions. It is almost invariably associated with other nutritional deficiencies or organic or psychological abnormalities which complicate the picture and make the diagnosis difficult. Quite often it is possible to make a correct diagnosis only after a therapeutic trial with thiamine, a procedure which is indicated wherever thiamine deficiency is suspected to exist.

It is probable, however, from the work of Swank and his associates that the administration of thiamine, even in uncomplicated thiamine deficiency, cannot be expected invariably to produce an amelioration of symptoms within a short period of time and, not too infrequently, almost complete therapeutic failure may result. The rapidity and degree of recovery from human thiamine deficiency with specific therapy probably varies, as with pigeons, inversely with both the chronicity and severity of the deficiency. Generally acute, severe deficiency can be expected to show a more satisfactory response to adequate therapy than chronic, relatively mild deficiences. The primary lesion is a biochemical or functional one and at this stage the disease is probably completely reversible; the greater the tissue destruction, the smaller the degree of recovery and the more protracted the recovery period.

VITAMIN C REQUIREMENT OF INFANTS

Clinical experience has shown that scurvy develops more frequently in artificially-fed infants than in those given human milk. Furthermore, formula-fed infants generally have lower plasma ascorbic acid values than do breast-fed babies, and take longer to have these levels increased to normal when supplementary amounts of ascorbic acid are given. Adequate consideration must be given, of course, to the fact that mother's milk is normally about four to five times higher in vitamin C content than even freshly drawn cow's milk. Two suggestions have been offered for apparent greater ascorbic acid requirement of artificially-fed infants: (1) formulas are usually boiled so that most of the ascorbic acid is destroyed, and (2) there may be some characteristic of cow's milk, particularly its greater protein content, which might be responsible. Recent work by Dann (*J. Clin. Invest.* **21,** *139 (1942)*) has suggested that the latter explanation is the correct one. Twenty-six premature babies were used for the study. One group received pooled human milk, the second was given formulas of cow's milk of isocaloric value. The milk was boiled in all cases, and samples were analyzed to make certain that ascorbic acid had been destroyed by boiling. Unless a contaminant such as copper is added, short periods of boiling do not necessarily destroy vitamin C in milk. Administration of a vitamin A and D concentrate was begun usually on the seventh day. When infants were able to take a full formula providing 120 to 125 calories per kg. of body weight per day (average age, ten days), 800 to 900 mg. of ascorbic acid were given in divided doses over a period of four or five days to "saturate" the tissues. Four infants also received an intramuscular injection of 100 mg. During the following five to eight days there were no additional sources of the vitamin. Then a "test" dose of ascorbic acid (either 100 mg. intramuscularly or 200 mg. orally) was given. Blood for determination of plasma ascorbic acid was obtained after four hours.

The fasting plasma ascorbic acid for both groups before the test dose was low, 0 to 0.5 mg. per cent except in one instance. Four hours after the test dose, the plasma of infants fed human milk contained 1.3 to 3.5 mg. per 100 ml., while that of the others ranged from 0.1 to 1.6 mg. per cent. All of the babies fed human milk showed a plasma increase after the test dose of at least 1.2 mg. per cent while only three of the infants who received cow's milk formulas were above this level. This higher rise in plasma ascorbic acid upon administration of a test dose has been shown previously by experimental studies to indicate a higher degree of tissue saturation. Therefore the response can be interpreted as indicating that the infants fed human milk were able to retain larger amounts of ascorbic acid.

The author suggested that there is either something in human milk which has a sparing action for vitamin C or that some component of cow's milk calls for a greater intake of the vitamin. The latter interpretation was preferred. There has been experimental work, particularly by Sealock and associates, to show that ascorbic acid is concerned with protein metabolism: (1) guinea pigs given tyrosine in their diets require more ascorbic acid than do controls, and (2) premature infants not given supplements of vitamin C excrete incompletely oxidized derivatives of phenylalanine and tyrosine. The premature infants fed breast milk in Dann's study received 2.6 to 2.8 g. of protein per kg. while the formula-fed babies received 4.6 to 6.1 g. per day. The investigation adds weight to the suggestion that the increased protein content of cow's milk formulas is responsible for the difference. Final proof, however, that this explanation is correct has not been provided.

NOTES

DR. GORTNER

Dr. Ross A. Gortner, Chief of the Division of Agricultural Biochemistry at the University of Minnesota and National President of Sigma Xi, died on September 30, 1942, of a heart ailment, at the age of 57. He was a recipient of the Osborne Medal in recognition of his outstanding researches in the field of cereal chemistry, and his text book "Outlines of Biochemistry" is recognized as one of the most authoritative books in this field. Dr. Gortner was an enthusiastic and versatile research worker, but many of his friends will feel that his greatest contribution to American chemistry was in his ability to inspire his associates and students with the ambition and desire to give their best efforts to high scholarship and research.

NUTRITION AND PUBLIC HEALTH

The American Public Health Association Year Book for 1941–42 mentions that nutrition is the field of public health where the most development has occurred recently. Further research and the increased application of newer methods and technics give promise of increased potentialities in good public health. Foundations and universities have recently exhibited a more effective interest in nutrition and its applications to problems of public health. The gap between the laboratory worker and the practicing physician is being narrowed and public health departments and other agencies are attempting seriously to utilize recently acquired concepts and technics.

COLONELS AND COOKS

An account of the organization dealing with "The Army's Nutritional Problems" is provided by Dr. James A. Tobey (*War Medicine* **2**, *437* (*1942*)). By an Act of Congress approved March 3, 1863, and further amended February 27, 1877, medical officers are required to unite with officers of the line in superintending cooking done by enlisted men. During the first World War a Division of Food and Nutrition was organized in the Surgeon General's office under the direction of an officer of the Sanitary Corps. At the present time Colonel Paul E. Howe is executive officer in charge of this phase of the Army's work.

BRITISH FOOD ADVISOR

Sir John Boyd Orr, noted British authority on nutrition, has been in the United States in an advisory capacity during the month of October and on October 27th, addressed a meeting of the American Public Health Association in Saint Louis.

HANDBOOK OF NUTRITION

Special articles on food and nutrition have been appearing in the current issues of the Journal of the American Medical Association. These articles have been prepared under the auspices of the A. M. A. Council on Food and Nutrition and will be published later as a Handbook of Nutrition.

THE RIGHT DIET

What is the right diet? Four separate answers to this question, in brief and interesting style, are given by Drs. McCollum, Heiser, Jolliffe, and Bessey (New York Times Magazine, Sept. 13, 1942). This article should be very helpful in the teaching of better nutrition to lay groups.

WARTIME NUTRITION

"We were told, when we tried to get vegetable salads into workers' canteens, to make good the loss of vitamin C which is almost unpreventable in large-scale cooking, that the 'hands' would not touch them. Wherever canteen supervisors have taken even moderate pains to encourage people to try salads—and I am speaking of wartime salads of shredded cabbage, grated carrot, potatoes, etc.—there has been a record of success." (Prof. J. C. Drummond in a paper read before the Royal Society of Arts, London, May 6, 1942.)

VITAMIN VALUES

Just published by the Bureau of Home Economics is "A Compilation of the Vitamin Values of Foods in Relation to Processing and Other Variants," with data from 34 journals through December 1940. This should be a valuable addition to the field of applied nutrition. The effects of cooking, canning, and dehydration on foods is receiving much consideration from nutrition workers at present and is one of the important phases of practical nutrition research.

RECENT NUTRITION BOOKS

Nutrition and Chemical Growth in Childhood. Vol. I, *Evaluation.* Icie G. Macy, Ph.D. Charles C. Thomas, Springfield, Ill. 1942. pp. 432.

Modern Bread from the Viewpoint of Nutrition. Henry C. Sherman and Constance S. Pearson. The Macmillan Co., N. Y. 1942. pp. 118.

Family Nutrition. The Philadelphia Child Health Society. April, 1942. pp. 106.